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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/774,706	02/09/2004	Lester F. Lau	05031.0008.NPUS01	2022

7590 11/14/2007

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EXAMINER	
POPA, ILEANA	
ART UNIT	**PAPER NUMBER**
1633	

MAIL DATE	DELIVERY MODE
11/14/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/774,706	LAU, LESTER F.	
	Examiner	Art Unit	
	Ileana Popa	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 August 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *10,16,19 and 21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *10, 16, 19, and 21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in the prior Office action.

2. Claims 1-9, 11-15, 17, 18, and 20 have been cancelled. Claims 16 and 21 have been amended.

Claims 10, 16, 19, and 21 are pending and under examination.

Response to Arguments

Claim Rejections - 35 USC § 112, enablement

3. Claims 19 and 21 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement, for the reasons of record set forth in the non-final Office action of 02/22/2007. Applicant's arguments filed 08/21/2007 have been fully considered but they are not persuasive.

Applicant traversed the instant rejection on the grounds that an *in vivo* animal model correlates with a specific condition if one of skill in the art would accept the model as reasonably correlating to the condition.

With respect to the rejection of claim 19, Applicant argues that the specification indicates that ASVD can be inherited as a single gene defect located within a 12 cM region located on chromosome 1(1p21-p31) and that the *CCN1* gene has been located and mapped to chromosome 1(1p21-p31) (paragraphs 0013 and 0029). Applicant argues Maslen actually supports the viability of the claimed transgenic mouse as a model for ASVD in all animals because it points out that some of the most powerful

means of identifying genes involved in heart development have been through genetically manipulating animal models, which provides information regarding the biochemical pathways that regulate atrioventricular septation (p. 207, column 2). Applicant argues that the Maslen's teachings do not apply to the instant model because the *CCN1*$^{+/-}$ mice do not display embryonic lethality, but rather display a phenotype that mirrors the human phenotype and therefore, avoids the pitfalls mentioned by Maslen. Applicant argues that Maslen's teachings of a single gene defect located in the same region of chromosome 1 as Cyr61 resulting in the disclosed phenotype (p. 206, column 1, second paragraph), of a putative cell adhesion protein as a susceptibility gene for AVSD (p. 206, column 2, first paragraph), and of AVSD being classified as a disease of the extracellular matrix (p. 207, column 2, last paragraph bridging p. 208) lead to the conclusion that the observed phenotype results from Cyr61 disruption. Additionally, Applicant argues that the portion cited by the Examiner from Scarff et al. refers to the retention of the selectable marker gene in knockout mice, and therefore, it is not relevant to the instant invention, which is drawn to mice in which the reporter gene has been knocked into the Cyr61 genomic sequence. Applicant argues that Scarff et al. teach that much less is known about the impact of the retention of the neomycin selectable marker on the expression of knock in reporter gene. Applicant argues that Scarff et al is one of the only three studies showing that selection of a neomycin cassette can alter the expression of GFP as a reporter gene and that there is no disclosure that retention of the neomycin cassette is capable of affecting expression of β-galactosidase. Applicant submits that each of the three studies teaches that the

retention of the neomycin cassette alters the expression level of the reporter gene and that the tissue specific expression patterns were not altered in mice bearing the neomycin cassette. Applicant argues that the Examiner failed to cite any art disclosing an altered phenotype arising from the retention of the neomycin gene. In view of al the arguments above, Applicant requests the rejection of claim 19 be withdrawn.

With respect to claim 21, Applicant submits that the Examiner mischaracterized Maslen. Applicant submits that, in the relevant part, Maslen teaches that ASVD can be inherited as a single gene defect (p. 206, column 1, second paragraph). Applicant points out that claim 21, as amended, specify a null mutation, i.e., a loss of function mutation and that the specification teaches through a working example that a null mutation results in a predisposition to the claimed phenotype. Applicant argues that one of skill in the art would understand that all null mutations are functionally equivalent and would predict that all null mutations would produce equivalent phenotypes. Therefore, Applicant argues, to the extent that the Examiner's reasoning with respect to the unpredictability of mutations in the *CCN1* gene, the rejection is now moot. Therefore, Applicant requests that the rejection of claim 21 be withdrawn.

Applicant's arguments are acknowledged, however, the rejection is maintained for the following reasons:

While Applicant's arguments regarding Scarff et al. are found persuasive, Applicant's arguments regarding Maslen are not. Applicant argues that, since the claimed transgenic mice do not show embryonic lethality, the Maslen's teachings do not

apply. This is not found persuasive because Maslen teaches that, although the complete elimination of a gene could provide information about the function of that gene in heart development, the same technique does not necessarily provide information about the function of the gene in AVSD pathogenesis. Maslen teaches that there are several knockout mouse models that have AVSD as phenotype that helped identifying genes involved in the endocardial cushion morhogenesis, however none of these models reflects the pathogenesis of the human disease because the complete elimination of a gene does not happen in the human disease, which is due to mutations and polymorphisms that do not completely eliminate the gene function (p. 208, column 2). It is noted that Applicant did not provide any evidence that severe defects, such as complete elimination of the gene, occurs in humans and is associated with the development of AVSD. The art does not provide such evidence. Moreover, neither the art not the specification teaches any mutation in the *CCN1* gene, wherein the mutation is responsible for AVSD. Therefore, one of skill in the art would recognize that the instant mouse could be useful to elucidate *CCN1* role in heart development, however, one of skill in the art would not recognize that such mice could be used to identify modulators of the AVSD development, since there is no evidence in the art and the specification that a deletion of the *CCN1* gene occurs in humans and lead to AVSD development. Therefore, one of skill in the art would not reasonably accept that the claimed animal model correlates to AVSD. Although it is true that Maslen teaches that chromosome 21 must comprise at least one gene that increases susceptibility to AVSD and that *CCN1* gene is located on chromosome 1p21-p31, in the absence of any

evidence by the Applicant that a severe defect such as deletion of the *CCN1* gene occurs in the human disease, the argument that one of skill in the art would recognize the correlation between the instant model could be used to screen for modulators of AVSD is not found persuasive.

With respect to the argument that Maslen teaches that a putative cell adhesion molecule is a susceptibility gene for AVSD, it is noted that Maslen refers to *CRELD1* and not *CCN1* (p. 206, column 2). With respect to the argument that Maslen teaches that AVSD is classified as a disease of Extracellular matrix, it is noted that Maslen teaches that, although AVSD has been previously classified as such, many different classes of molecules other that extracellular matrix components can contribute to the AVSD pathogenesis (p. 208, column 1).

The same considerations above apply to claim 21, since, with the exception of the claimed mice wherein the mutation is introduced in laboratory, there is no evidence that a null mutation in a *CCN1* allele occurs in nature wherein the mutation is correlated with AVSD in any animal.

Claim Rejections - 35 USC § 102

4. The rejection of claims 1 and 4 under 35 U.S.C. 102(b) as being anticipated by Mo et al. (Mol Cell Biol, 2002, 22: 8709-8720) is moot since Applicant cancelled the claims in the response filed on 08/21/2007.

5. Claims 10 and 16 remain rejected under 35 U.S.C. 102(b) as being anticipated by Mo et al. for the reasons of record set forth in the non-final Office action of 02/22/2007. Applicant's arguments filed 08/21/2007 have been fully considered but they are not persuasive.

Applicant traversed the instant rejection on the grounds that Mo et al. do not describe any cardiovascular defect and do not attempt to characterize the *CCN1*$^{+/-}$ mice. Applicant argues that Mo et al. only teach that the *CCN1*$^{+/-}$ mice are viable and fertile and that, since the instant specification teaches that the *CCN1*$^{+/-}$ mice do not exhibit any apparent phenotype, the discovery the detection of AVSD in the *CCN1*$^{+/-}$ mice was surprising (paragraph 0070). Therefore, Applicant argues, one of skill in the art would have no motivation to test the *CCN1*$^{+/-}$ mice for the presence of AVSD and that the Examiner lacks a basis in fact or technical reasoning to rely on inherency to support a detection of AVSD in the *CCN1*$^{+/-}$ mice. Applicant continues arguing that, even if Mo et al. teach analyzing β-galactosidase expression in the *CCN1*$^{+/-}$ mice by in situ hybridization and immunocytochemistry, such disclosure would not necessarily have resulted in the AVSD detection because the specification teaches that 35% of the *CCN1*$^{+/-}$ mouse embryos do not exhibit the AVSD phenotype (paragraph 0071). Applicant submits that analyzing β-galactosidase expression in any of the *CCN1*$^{+/-}$ mouse embryos not exhibiting the phenotype would not have resulted in the determination of AVSD, and therefore, such determination cannot necessarily flow from the teachings of Mo et al. Therefore, Applicant requests the withdrawal of the rejection.

Applicant's arguments are acknowledged, however, the rejection is maintained for the following reasons:

The argument that the specification teaches that the *CCN1*$^{+/-}$ mice do not exhibit any apparent phenotype and therefore, one of skill in the art would not have been motivated to test for these mice for the presence of AVSD is irrelevant because Mo et al. already teach testing *CCN1*$^{+/-}$ mouse embryos by immunohistochemistry, i.e., they go beyond the "apparent phenotype". Moreover, this is a 102 rejection and the argument of lack of motivation is inappropriate. The teaching is in the prior art (see also the non-final Office action of 02/22/2007). The argument that that 35% of the *CCN1*$^{+/-}$ mouse embryos do not exhibit the AVSD phenotype is not found persuasive because Mo et al. teach testing a large number of embryos and not one embryo; since 65% of these embryos exhibit AVSD, this phenotype would have been necessarily identified by their procedure (i.e., the procedure would detect the defect) (p. 8710, column 1, third full paragraph, Table 1). The phenotype of transgenic or knockout mice is established by testing a large number of animals; this is the routine practice in the art, not the testing of only one animal. Therefore, identification of the AVSD in the *CCN1*$^{+/-}$ mice is inherent in the teachings of Mo et al. and the rejection is maintained.

Conclusion

6. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ileana Popa whose telephone number is 571-272-5546. The examiner can normally be reached on 9:00 am-5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Ileana Popa, PhD

SUMESH KAUSHAL, PH.D.
PRIMARY EXAMINER
11/18/07